

Variable presentations of radiation-associated angiosarcoma in patients treated for breast cancer

Samreen Khan, Steven Goh

ABSTRACT

Introduction: Radiation-associated angiosarcoma is a rare and late complication of radiotherapy in breast cancer. Its incident is reported in the range of 0.03–0.3%. It carries a poor prognosis with a 5-year survival rate of 43–54%. Due to its non-specific presentation, diagnosis is often delayed.

Case Series: Case 1: A 60-year-old female presented six years after her breast cancer treatment with a history of bruising over the breast following trauma. Initial imaging and punch biopsy only showed inflammatory change. Her breast symptoms progressed and repeat biopsy revealed angiosarcoma. She was treated with chemotherapy followed by mastectomy.

Case 2: A 60-year-old female treated for breast cancer, presented two and a half years later with subtle erythema over the breast. Imaging was normal. Punch biopsy showed angiosarcoma and she underwent mastectomy.

Case 3: A 90-year-old female presented eight years after treatment for breast cancer. Her symptoms included blisters over the breast that bled at times. Punch biopsy showed angiosarcoma. There was rapid disease progression with convergence of the blisters into a large necrotic mass. She underwent a mastectomy for local control. The angiosarcoma recurred a year later and she died within three months of recurrence.

Conclusion: Radiation-associated angiosarcoma is rare but carries a poor prognosis. Due to its non-specific

presentation, diagnosis is often delayed. A high level of suspicion is needed in patients presenting with unusual breast symptoms and changes post-treatment.

Keywords: Breast cancer treatment, Breast radiotherapy, Radiation-associated angiosarcoma

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INTRODUCTION

Radiation-associated angiosarcoma is a rare and late complication of radiotherapy in breast cancer. With the advent of breast conservation and adjuvant radiotherapy (RT), soft tissue sarcoma especially angiosarcoma has elevated risk in breast cancer patients [1]. Its incident is reported in the range of 0.03–0.3% [2–5]. Radiation-associated angiosarcoma arises after a latent period of median 7.5 years, with studies showing it to range from 1 to 26 years [4, 5]. Radiation-induced angiosarcoma is defined as per Cohan and modified by Arlen which includes (1) previous history of radiotherapy with (2) a latent period of more than 3–4 years, (3) development of sarcoma in the area of previous irradiation or the area adjacent to it, and (4) histological distinction between the primary cancer and the secondary angiosarcoma.

It carries a poor prognosis with a 5-year survival rate of 43–54% [5–7]. Due to its non-specific presentation, diagnosis is often delayed. It requires a prolonged follow-

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up and a high index of suspicion to be picked up early. High grade and larger tumor size carry a worse prognosis [6, 7]. Treatment is along the lines of soft tissue sarcoma. Due to its low incidence rate, no randomized prospective studies exist on the subject and there are no clear guidelines on optimal treatment regimens.

We present three cases of radiation-associated angiosarcoma of breast, seen at our institution during a 10-year period. We aim to highlight its heterogeneous presentation and the need for a high index of suspicion.

CASE SERIES

Case 1

This 60-year-old female had treatment for left breast cancer in 2010 (Table 1). In December 2015, she presented with bruising over left breast with preceding history of heavy lifting. Ultrasound showed mild soft tissue edema. On clinical review at three months the changes persisted and punch biopsy was taken. It showed chronic inflammatory changes. Further clinical review in June 2016 revealed persistent bluish discoloration now extending to whole of breast. Repeat biopsy showed angiosarcoma (Table 2). The breast changes quickly progressed and she was treated with neo-adjuvant chemotherapy followed by mastectomy. She remains under surveillance, four years post-treatment for angiosarcoma.

Case 2

A 60-year-old female initially treated for a screen detected breast carcinoma in 2017 (Table 1), presented in July 2020 with persistent redness over lower half of right breast. It had felt hot initially but was not itchy

or painful. On examination she had a 50 mm area of subtle erythema over the lower aspect of the right breast (Figure 1). Mammogram did not show any suspicious features. Ultrasound showed 5 mm skin thickness with normal axillary lymph nodes. Punch biopsy revealed angiosarcoma. She was treated with completion right mastectomy in August 2020. Final histology showed a 60 mm, low grade angiosarcoma, with clear resection margins. No further treatment was given (Table 2). She is on surveillance and found to be disease free two years post-treatment for angiosarcoma.



Figure 1: Case 2: Presentation with subtle erythema over lower breast.

Table 1: Breast cancer diagnosis and treatment

Case	Tumor biology	Surgery	Adjuvant treatment	Radiotherapy
1	IDCa, G2, 20 mm, DCIS, 1 LN (micromet), ER 8, Her2 negative	WLE and SLNBx followed by ANC	Adjuvant chemotherapy. Completed five years of endocrine treatment	Radiotherapy given at another hospital, Dec 2010
2	IDCa, G2, 14 mm, DCIS, ER 8, Her2 negative	WLE and SLNBx	On endocrine treatment	40 Gray in 15 fraction, Jan 2018
3	IDCa, G2, 7 mm, ER 8, Her2 negative	WLE and SLNBx	Completed five years of endocrine treatment	40 Gray in 15 fractions, Oct 2012

Abbreviations: ANC: axillary node clearance; DCIS: ductal carcinoma in situ; ER: estrogen receptor; G: grade; Her2: human epidermal growth factor receptor 2; IDCa: invasive ductal carcinoma; SLNBx: sentinel lymph node biopsy; WLE: wide local excision

Table 2: Radiation-associated angiosarcoma diagnosis and treatment

Case	Latency period (years)	Presentation	Treatment
1	5.5	Bruising, persistent, rapid progression	Chemotherapy followed by mastectomy
2	2.5	Subtle persistent redness lower half of breast	Mastectomy
3	7.5	Purple/red blotches, blisters, rapid progression	Mastectomy, recurrence

Case 3

A 90-year-old female diagnosed with right breast cancer in 2012 (Table 1). She presented in April 2020, with a 10-day history of a bleeding ulcer over her right breast. She was found to have multiple red/purple patches and blisters over the breast. Mammogram and ultrasound showed new diffuse skin thickening of right breast with multiple nodular areas of skin thickening (Table 2). Normal axilla. Punch biopsy was taken.

In the meantime, the lesion progressed rapidly and at the time of surgery it had turned into a large, protuberant, ulcerating mass (Figure 2A). There was rapid progression of disease (Figure 2B). A palliative mastectomy was performed in June 2020. Histology confirmed radiation-associated angiosarcoma, 70 mm, with tumor invading skin and a 10 mm satellite lesion. It was completely excised. No further chemotherapy or radiotherapy was planned. She presented 12 months after surgery with local recurrence (Figure 2C). She was referred for palliative care but died within three months.



Figure 2: (A) Case 3—One month after initial symptoms. Progressive coalescence of skin blebs into a necrotic mass. (B) Two months after initial presentation. (C) Recurrence of skin blebs, 12 months after mastectomy.

DISCUSSION

Radiation-induced angiosarcoma of the breast is a rare but increasingly significant pathology. The current treatment of early breast cancer renders the prompt and timely diagnosis of this tumor an important clinical concern.

At presentation the clinical signs are often mimicked by post-RT changes [8]. It can present as painless bruising or often as multifocal, purplish discoloration, eczematous rash, hematoma-like swelling, and diffuse breast swelling [9].

Our patients demonstrated these varied presentations. Two of our cases showed rapid progression.

Baseline investigations revealed non-suspicious feature in all our patients. Punch biopsy confirmed the histological diagnosis. A high index of suspicion with early routine imaging utilizing magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) has been recommended for early detection [9].

Surgical excision with a negative margin remains the mainstay of treatment [10]. There is a debate on whether mastectomy is necessary in all cases of radiation-associated angiosarcoma of the breast. An analysis of the SEER database, published in 2017, Yin et al. found no significant improvement in survival between breast conserving surgery (BCS) and mastectomy groups [11].

We have not offered further radiotherapy to our patients. However it is a modality that can be utilized although no guidelines exist on its benefit and optimum dosage. Yin et al. recommended that routine radiation in unselected breast angiosarcoma should be cautious because there is at least no survival benefit [11]. On the other hand, a recent meta-analysis by Yara Abdou et al. reported that the patients who had surgery plus RT had improved recurrence free survival compared to surgery alone [7]. The findings echoed Depla's earlier systematic review that reported surgery with radiotherapy had a better 5-year local recurrence free interval (LRFI) of 57% compared to 34% for surgery alone ($p=0.008$) [6]. In the more recent Dutch study, the addition of radiotherapy did not show a survival benefit in the treatment of radiation associated angiosarcoma (RAAS) [3].

Among soft tissue sarcomas, angiosarcomas are found to be more sensitive to cytotoxic chemotherapy [12]. Angiosarcomas have shown to be particularly sensitive to taxanes and liposomal doxorubicin [13, 14].

Targeted agents such as vascular endothelial growth factor (VEGF) inhibitors and agents targeting non-VEGF angiogenic pathways are being studied as another effective modality. Angiosarcoma response to these agents has been limited and search for effective combination continues.

Doxorubicin-based chemotherapy remains the first line treatment for metastatic or un-resectable angiosarcoma with a progression-free survival of 3.7–5.4 months [15].

The low incidence rate of radiation-associated angiosarcoma renders prospective randomized trials unlikely. A retrospective multicenter audit Breast Angiosarcoma Surveillance Study (BRASS) is open for data collection in the UK. It aims to generate data to help guide practice guidelines in the future [16].

CONCLUSION

Due to its prolonged latency period, a longer follow-up of patients who have received radiotherapy is

warranted. A high level of suspicion is needed in patients presenting with unusual breast symptoms and changes post-treatment. In the era of early discharge and patient directed follow-up, patients should be informed of this rare but potentially fatal condition.

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Author Contributions

Samreen Khan – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Steven Goh – Conception of the work, Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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